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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/076,571	02/19/2002	Michael R. Johnson	213706US96	1283

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EXAMINER	
MCKENZIE, THOMAS C	
ART UNIT	**PAPER NUMBER**
1624	9

DATE MAILED: 09/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/076,571	JOHNSON, MICHAEL R.	
	Examiner	Art Unit	
	Thomas McKenzie Ph.D.	1624	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 14-124* is/are pending in the application.

4a) Of the above claim(s) *88-118* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-11,57-60,84,87 and 119-124* is/are rejected.

7)☒ Claim(s) *8,14-56,61-83,85 and 86* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4&6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to an election filed on 8/7/03. There are one hundred twenty-two claims pending and ninety-one under consideration. Claims 1-11, 14-85, and 119-124 are compound claims. Claim 86 is a composition claim. Claim 87 is a use claim. This is the first action on the merits. The application concerns some acyl guanidine linked compounds, compositions, and uses thereof.

Election/Restrictions

2. Applicant's election with traverse of Group VII, the phenyl compounds, and claim 87, the hydration method in Paper No. 8 is acknowledged. The traversal is on the ground(s) that no search burden is present. This is not found persuasive because according to MPEP §803 "For purposes of the initial requirement, a serious burden on the examiner may be *prima facie* shown if the examiner shows by appropriate explanation of separate classification, or separate status in the art, or a different field of search as defined in MPEP § 808.02. That prima facie showing may be rebutted by appropriate showings or evidence by the applicant." Applicants pointed to no errors in the Examiners analysis of the classification of the different inventions. The requirement is still deemed proper and is therefore made FINAL.

3. Claims 88-118 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable

generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8.

Title

4. After restriction, the title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: addition of the phrase "Phenyl Guanidine" at the beginning of the title.

Abstract

5. Applicant is reminded of the proper content of an abstract of the disclosure. A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details. The abstract is too short and generic. Examiner suggests claim 1, lines 1-25 including the figure, and the utility.

Drawings

6. Applicants have submitted two pages of drawings but the Examiner can find no brief description of these drawings in the specification.

Claim Rejections - 35 USC § 112

7. Claim 87 is rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for promoting hydration of

mucosal surfaces. The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims. "The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546.

a) Determining if any particular claimed compound would promote hydration of mucosal surfaces would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with a number of fundamentally different pulmonary diseases described below, or to testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a large degree of experimentation. b) The direction concerning promoting hydration of mucosal surfaces is found in lines 8-10, page 3 and the passage spanning line 32, page 22 to line 2, page 23, which merely states Applicants' intention to do so. Applicants describe formulations in lines 15-18, page 23 and lines 1-9, page 25. There are no working examples of any formulated

product. Doses required to practice their invention are described in lines 13-18, page 27 and the passage spanning line 26, page 27 to line 4, page 28. A 2,000-fold range of doses is recommended. There is a *in vitro* assay drawn to blocking sodium channels described in the passage spanning line 15, page 29 to line 11, page 30 with data for 15 compounds. It is unclear if this assay is correlated to promoting hydration of mucosal surfaces. Applicants do not assert so and it is not art-recognized as being so correlated. There is an *in vivo* assay for mucociliary clearance in sheep described in lines 16-19, page 32 with data for compound Ia. This assay would appear to be unrelated to promoting hydration of mucosal surfaces. c) There is no working example of treatment of any disease in man or animals. d) The nature of the invention is clinical treatment of disease, which involves physiological activity. e) The state of the clinical arts in mucosal hydration is provided by Barrett (Annu. Rev. Physiol.) who reports that chloride ion, not the sodium ion measured by Applicants, is the "major determinant of mucosal hydration", in the abstract. While chloride anion is often accompanied by sodium cation, both potassium and calcium are also important balancing counter ions. A transporter that moves both sodium and potassium, presumably in equal amounts is discussed in the paragraph spanning pages 542-543. Potassium channels and their role in chloride transport are discussed on page 544. An

atypical, and less understood calcium channel, which moves chloride is discussed on page 547.

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The scope of the claims involves all of the thousands of compounds of claim 1. The term "promoting hydration of mucosal surfaces" reads on promoting hydration in sick mammals with below normal mucosal surface hydration, promoting hydration in sick mammals with normal mucosal surface hydration, promoting hydration in sick mammals with above normal mucosal surface hydration, for example in someone suffering from edema. The latter would appear dangerous. It would read on doing these things in well, asymptomatic mammals. The specification fails to teach any benefit to be gained from such actions. Thus, the scope of claim is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to

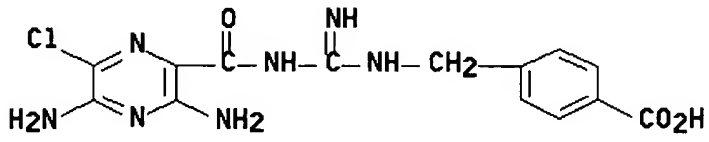
make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Claim Rejections - 35 USC § 102

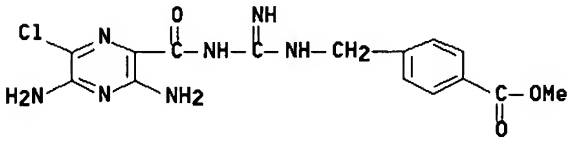
8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7, 9-11, 57-60, and 84 are rejected under 35 U.S.C. 102(b) as being anticipated by Kleyman (American Journal of Physiology). The compound shown below fits formula (I) with X = chlorine, Y = $N(R^2)_2$, $R^1 = R^2 = R^3 = R^6 = R^7 = R^L$ = hydrogen, R^4 = (A), o = n = 0, x = a bond, p = 1, and $R^5 = -(CH_2)_n-CO_2R^7$. It has Registry Number 133481-24-0 and is found in Table 1, page C272 of the reference. It is compound 3 and is described in the third paragraph, first column, and same page as a gift from Merck. Thus, this is an enabling reference.



9. Claims 1-7, 9-11, 57-60, 84, and 119-124 are rejected under 35 U.S.C. 102(b) as being anticipated by Cocks (British Journal of Pharmacology). The compound shown below fits formula (I) with X = chlorine, Y = $N(R^2)_2$, R^1 = R^2 = R^3 = R^6 = R^7 = R^L = hydrogen, R^4 = (A), o = n = 0, x = a bond, p = 1, R^5 = -$(CH_2)_n$-CO_2R^7, and R^7 independently = methyl. It has Registry Number 117241-68-6 and is found in Table 1, page 69 of the reference. It is the sixth entry in the Table and is compound G_5. Synthesis of the compound is taught in the first paragraph on the same page.



Allowable Subject Matter

10. Claims 8, 14-56, 61-83, 85, and 86 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

11. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for amendments is (703) 872-9306. The PTO presently encourages all applicants to communicate by FAX.

The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, you can reach the Examiner's supervisor, Mukund Shah at (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

Thomas C. McKenzie, Ph.D.
Patent Examiner
Art Unit 1624

TCMcK

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